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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,097	10/13/2005	Paul King	NREL 03-11	4772
<p>7590 03/22/2007</p> <p>Paul J White Nrel 1617 Cole Boulevard Golden, CO 80401</p>			<p>EXAMINER</p> <p>CHOWDHURY, IQBAL HOSSAIN</p>	
			<p>ART UNIT</p> <p>1652</p>	<p>PAPER NUMBER</p>
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		03/22/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/553,097	Applicant(s) KING ET AL.	
	Examiner Iqbal H. Chowdhury, Ph.D.	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 January 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 27-45 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 27-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 October 2005 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>10/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application is a 371 of PCT/US04/11830.

The preliminary amendment filed on 1/4/2007 adding new claims 27-45 and canceling claims 2-26 is acknowledged. Claims 1 and 27-45 are currently pending in the instant Office action.

Election/Restriction

Applicant's election of Group I, Claims 1-3, in the reply filed on 1/3/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

However, in lieu of making an election under 35 U.S.C. 121, applicants had a telephonic interview on December 4, 2006 with the Examiner for electing a Group of inventions as restricted by the Examiner, which was mailed on 11/3/2006. During the interview applicants proposed submitting a new set of claims and Examiner agreed.

Therefore, claims 1 and 27-45 are now pending and under consideration.

Priority

Acknowledgement is made of applicants claim for priority of provisional application 60/464,081 filed on 4/18/2003.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/13/2005 was filed with the National Stage Application. The submission is in compliance with the provisions of 37

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CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. The signed copy of IDS is enclosed herewith.

Drawings

Drawings submitted on 10/13/2005 are objected by the Examiner for the recitation of the nucleic acid and protein sequences without appropriate sequence identifiers i.e. SEQ ID NOs. Examiner urges the applicants to provide sequence identifiers in response to this Office action. See particularly 37 CFR 1.821(d).

Non-compliance of Sequence Rule

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that Specification (p23, paragraph 3) recites the nucleic acid sequence without a corresponding sequence identifier. See particularly 37 CFR 1.821(d).

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 29-34, 36 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 29-31, 34, 36, and 43 recite “bulky” or “bulky residue” which is unclear. This is an unfamiliar or non-scientific way of describing an amino acid. The metes and bounds of the term “bulky” or “bulky residue” are not clear to the Examiner.

It is not clear whether the phrase “bulky” or “bulky residue” continues to have the properties of a specific kind of amino acid residues. The Examiner requests clarification.

Claims 41 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 41 and 42 recite “average --- size” with two numbers, which is confusing. Since averages usually a single number or value, the phrase “average --- size” in the context here is confusing. The Examiner requests clarification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 27-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 27-45 are directed to any oxygen-resistant iron hydrogenase derived from an oxygen sensitive iron hydrogenase by the substitution of one or more amino acid residues within the hydrogen channel of the oxygen-sensitive iron hydrogenase.

The Court of Appeals for the Federal Circuit has recently held that a “written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula [or] chemical name,’ of the claimed subject

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matter sufficient to distinguish it from other materials.” *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical*).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described (this is in contrast to a single representative species disclosed in the specification, i.e. HydA1), the same analysis applies wherein the product, used in the claimed methods, must have adequate written description (see *Enzo* paraphrase above).

Thus, claims 1 and 27-45 are drawn to any oxygen-resistant iron hydrogenase derived from any oxygen sensitive iron hydrogenase by the substitution of one or more amino acid residues within the hydrogen channel of any oxygen-sensitive iron hydrogenase from any source. Claims are drawn to an enzyme whose structure is not fully described in the specification. No information, beyond the characterization of hydrogenase having activity of producing hydrogen

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gas in living cell has been provided, which would indicate that applicants had possession of the claimed genus of any hydrogenase enzyme. The specification does not contain any disclosure of the structure of all the mutants or variants of all hydrogenase enzymes within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including mutants and variants having different structures. Therefore, many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses the structure of only a single representative species of the claimed genus i.e. HydA1 from Chlamydomonas reinhardtii, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1 and 27-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an oxygen resistant iron hydrogenase obtained by substitution of amino acid lining the hydrogen channel with Trp, Ile, Leu, or Phe in the HydA1 dehydrogenase, which is oxygen-sensitive (isolated from *Chlamydomonas reinhardtii*) for use in the bulk production of hydrogen gas, does not reasonably provide enablement for any such oxygen-resistant mutant iron hydrogenases derived from any or all oxygen-sensitive iron hydrogenases by substituting one or more amino acid residues within the hydrogen channel with any or all amino acid residues. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731,737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows:

(1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The factors, which have, lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed below:

The breadth of the claims:

Claims 1 and 27-45 are so broad as to encompass any oxygen-resistant iron hydrogenases derived from any oxygen-sensitive iron hydrogenases by substituting one or more amino acid residues within its hydrogen channel with any or all amino acid residues. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of oxygen-resistant iron hydrogenase and the different amino acids for substitution broadly encompassed by the claims. However, in this case the disclosure is limited to the variants of a single oxygen resistant hydrogenase obtained by substituting the amino acid lining the hydrogen channel with Trp, Ile, Leu or Phe.

The amount of direction or guidance presented and the existence of working examples:

The specification discloses specific mutant of iron hydrogenase (oxygen-resistant) by substitution mutation, derived from oxygen-sensitive HydA1, isolated from *Chlamydomonas*

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reinhardtii for use in the bulk production of hydrogen gas. However, the specification fails to provide any clue as to the structural elements required in any oxygen-resistant iron hydrogenases derived from any oxygen-sensitive iron hydrogenases by substituting one or more amino acid residues within the hydrogen channel of with any amino acids as for successfully practicing the claimed invention. No correlation between structure and function has been presented.

Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any oxygen-resistant iron hydrogenases derived from any oxygen-sensitive iron hydrogenases by substituting one or more amino acid residues within the hydrogen channel of any oxygen-sensitive iron hydrogenases from any source. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any oxygen-resistant iron hydrogenases derived from any oxygen-sensitive iron hydrogenases by substituting one or more amino acid residues within the hydrogen channel with any or all amino acid such that said variant has the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art:

The amino acid sequence of a polypeptide determines its structural and functional properties. While the art discloses a single HydA1 protein, neither the specification nor the art provide a correlation between structure and function of the amino acid residues in the lining of

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hydrogen channel such that one of skill in the art can envision in changing the amino acid residues in the lining of the hydrogen channel of any oxygen-resistant iron hydrogenases derived from any oxygen-sensitive iron hydrogenases, which would impose undue burden to make a mutant hydrogenase that is oxygen resistant using any or all oxygen sensitive hydrogenase. In addition, there is no teaching or suggestion in the specification as to how the structure of the any hydrogenase protein correlates with HydA1 protein or corresponding mutants, the degree of structural similarity among all HydA1 proteins with respect to Chlamydomonas HydA1 protein known in the art.

Conclusion:

Therefore, taking into consideration of the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

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international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 27-29, 31-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Dillon et al. (US PGPUB 2007/0009942 A1, publication 1/11/2007, claim priority of US copending application 10/411,910 filed on 4/12/2003). Instant claims are drawn to any oxygen-resistant iron hydrogenase derived from any oxygen sensitive iron hydrogenase by the substitution of one or more amino acid residues including tryptophan, isoleucine, leucine or phenylalanine within the hydrogen channel of any oxygen-sensitive iron hydrogenase.

Dillon et al. teach an oxygen-resistant or tolerant iron hydrogenase derived from oxygen sensitive hydrogenase i.e. hydrogenase activity is inhibited by the presence of oxygen, capable of producing hydrogen, which also contained nickel ion in addition to iron in the active site i.e. the hydrogenase comprises iron and nickel ion having bimetallic active site. Dillon et al. also teach substitution of one or more amino acid residues in the hydrogen channel region near active site comprising $FX^1X^2X^3G^1G^2VMEA^1A^2X^4R$ region of the hydrogenase protein, wherein X can be any amino acid substituted with any amino acid. Dillon et al. further teach substitution of amino acid phenylalanine, glycine, valine, methionine, glutamic acid, alanine, arginine and glutamine into the gas channel segment, in the amino acid sequence (abstract, p1, Col 1-2, p4, Col 1-2, p18).

Because the iron hydrogenase of the instant application and that of the reference is one and the same, and the same amino acids are involved in substituting of amino acid in the hydrogen channel, Examiner takes the position that the hydrogen channel diameter of hydrogen channel as disclosed by the instant application would be inherently possessed by the hydrogenase

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protein of the reference. Since the Office does not have the facilities for examining and comparing applicants' protein diameter with the diameter of protein disclosed by the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product diameter (i.e. protein diameter) and the product diameter of the prior art (i.e., protein diameter). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594. Therefore, Dillon et al. anticipate claims 1 and 27-45 of the instant application.

Conclusion

Status of the claims:

Claims 1 and 27-45 are pending.

Claims 1 and 27-45 are rejected.

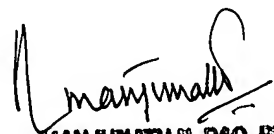
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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